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Durable strategies to deploy plant resistance in agricultural landscapes

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Summary

• The deployment of resistant crops often leads to the emergence of resistance-breaking pathogens that suppress the yield benefit provided by the resistance. Here, we theoretically explored how farmer main leverages (resistant cultivar choice, resistance deployment strategy, landscape planning, cultural practices) can be best combined to achieve resistance durability while minimising yield losses due to plant viruses.
• Assuming a gene-for-gene type of interaction, virus epidemics are modelled in a landscape composed of a mosaic of resistant and susceptible fields, subjected to seasonality, and of a reservoir hosting viruses year round. The model links the genetic and the epidemiological processes shaping at nested scales the demo-genetics dynamics of viruses.
• The choice of the resistance gene (characterized by the equilibrium frequency of the resistance-breaking virus at mutation-selection balance in a susceptible plant) is the most influential leverage of action. Our results showed that optimal strategies of resistance deployment range from mixture (where susceptible and resistant cultivars coexist) to pure strategies (with only resistant cultivar) depending on the resistance characteristics and on the epidemiological context (epidemic incidence, landscape connectivity).
• We demonstrate and discuss gaps concerning virus epidemiology across the agro-ecological interface that must be filled to achieve sustainable disease management.

Keywords: Deployment strategy; Durable resistance; Evolutionary epidemiology; Gene-for-gene model; Landscape epidemiology.

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Introduction

The breakdown of genetic resistance by plant pathogens is a particularly spectacular case of disease emergences where new resistant genes can be impaired in a few years or months (for review, see McDonald & Linde (2002) for fungal pathogens and García-Arenal & McDonald (2003) for viruses). These emergences impact food production and are associated with environmental issues as alternative control methods often rely on pesticides. Thus promoting durable resistance, defined by R. Johnson (1979) as resistance remaining effective in a cultivar for a long period of time during its widespread cultivation, is still an ongoing quest.

Resistance or susceptibility of plants to pathogens often results from a molecular relationship governed by a gene-for-gene interaction (Flor, 1971). For qualitative resistance gene (i.e. resistances that prevent any plant infection), the interaction between the resistance gene of the plant (with at least two allelic forms: 'resistant' and 'susceptible') and the avirulence gene of the pathogen (with at least two allelic forms: "wild-type" and "resistance-breaking" (RB)), determines the resistance or susceptibility of the plant. Since the earlier work of Leonard (1977), the evolution of host resistance and pathogen pathogenicity (i.e. its ability to cause disease on a particular host) in gene-for-gene interactions has been the subject of much research highlighting how multiple locus interaction (e.g. Sasaki, 2000; Segarra, 2005; Tellier & Brown, 2007), genetic drift (e.g. Kirby & Burdon, 1997; Salathé *et al*., 2005), or spatial structuring of populations (e.g. Thrall & Burdon, 2002) impact the coevolution between plants and pathogens in natural conditions. A comprehensive review of the entire subject has recently been published by Brown & Tellier (2011). These works often do not apply to the management of resistance durability as agricultural practices, by imposing the genetic composition and spatial distribution of fields, disrupt natural coevolution and drives the coevolution of crops and pathogens to instability (Sun & Yang, 1998, 1999).

Earlier research deriving durable strategies of resistance deployment steamed from modeling approaches in population genetics where durability was assessed by the frequencies of the RB pathogen genotype (for review, see van den Bosh & Gilligan, 2003; Gilligan, 2008). Assuming that the RB genotype was pre-existing and disregarding the yield benefit provided by resistant crops, these works traditionally advise to introduce resistance genes at a low cropping ratio (i.e. at low frequency) (Pink & Puddephat, 1999). Since then, pathologists have widely recognized that considering the interactions occurring across scales between evolutionary and epidemiological processes greatly improve our understanding of disease emergence (Galvani, 2003; Day and Proulx, 2004; Jeger *et al*., 2006; Mideo *et al*., 2008). Van den Bosh & Gilligan (2003) were the first to propose a model linking population dynamics and population genetics to re-investigate the question of resistance durability. By introducing two new measures of durability, they showed that (i) resistance durability can also be extended by high cropping ratios if the RB genotype is not preexisting and that (ii) the additional yield provided by a resistant cultivar is only slightly dependent on the cropping ratio. These conclusions rely on two main assumptions: (i) no fitness cost is needed to overcome the resistance and (ii) continuous planting and harvesting.

In the present study, we developed and analysed a model relaxing these two assumptions. Fitness costs associated to resistance breakdown, although not systematic, occur in many plant-pathogen interactions and especially for plant viruses (Sacristan & García-Arenal, 2008) where they are often high (Carrasco *et al*., 2007; Sanjuán, 2010; Fraile *et al*., 2011). Plant virus studies also indicate that 1 or 2 nucleotide substitutions in avirulence genes are often sufficient to break resistance down (Harrison 2002; Lecoq *et al*., 2004; Kang *et al*., 2005). These 2 factors, fitness costs and numbers of mutation, along with the mutation rate determine the equilibrium frequency of

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RB mutants in a virus population (Ribeiro *et al.*, 1998). It corresponds to the mutation-selection balance. The seasonality of planting and harvesting activities is the rule in most agricultural systems and largely impacts epidemic dynamics as well as pathogen evolution (for a review based on modelling approaches, see Mailleret & Lemesle, 2009; Hamelin *et al.*, in press). Wild or weedy plant species that act as a "reservoir" of inoculum by providing a "green bridge" between the maturity of one crop and the sowing of the next are important for pathogen dynamics and evolution (Burdon & Thrall, 2008). Our model simulates the three steps of the breakdown of a qualitative resistance: (i) at the scale of the cells of a susceptible host, mutations in the avirulence gene of a virus generate RB variants, (ii) at the host scale, the RB variants must be sufficiently competitive to invade their host and increase their frequency and (iii) at the landscape scale, the RB variants should spread between hosts and fields to cause the breakdown of the resistance.

From an applied perspective, the analyses presented are designed to provide guidelines for farmers aiming altogether to optimise the deployment of a resistant cultivar in a landscape over several years. To achieve this goal, we will answer the following questions: (i) What is the relative efficiency of the farmer main leverages (choice of resistant cultivar, implementation of a cropping ratio, use of cultural practices, use of landscape planning policies) on the yield increase provided by the deployment of a resistant cultivar? (ii) Which cropping ratio maximizes the additional yield provided by the resistance? From a basic perspective, the analyses reveal the relative importance of epidemiological, genetic and evolutionary factors in pathogen emergence.

Model description

Model overview. The model is an extension of the well-known epidemic models introduced by Kermack & McKendrick (1927). Two virus variants ("wild-type" and "resistance breaking" (RB)) and two cultivated host genotypes ("susceptible" (S) and "resistant" (R)) are considered in a gene-for-gene interaction system. The S cultivar can be infected by both virus variants while only the RB variant can infect the R cultivar. The model simulates the epidemiology of a viral disease during n_y years ($1 \leq y \leq n_y$) in a seasonal landscape made up of a cultivated and a reservoir compartments. Epidemic dynamics in annual crops are represented as well as the flow of virus from the reservoir hosts to crops and back to the reservoir. Viral epidemics spread in a metapopulation of hosts composed of n_f fields (representing patches) and of one reservoir. Three routes of infection are considered in this landscape: (i) between the reservoir and the fields, (ii) between fields and (iii) within a field. Fields are sown with n_p plants of either a susceptible (S) or a resistant (R) cultivar. n_f^S and n_f^R fields are sown with each cultivar, the proportion of resistant fields (termed cropping ratio) being φ. As crops are cultivated during n_d days per year ($0 \leq t \leq n_d$), fields disappear from the landscape at the end of each cropping seasons. By contrast, the reservoir hosts the virus population year round and allows virus to overwinter. It reflects with some delay the demo-genetic dynamics of the viral populations issued from the fields. The description of the seasonality leads us to use a semi-discrete modelling approach (Mailleret & Lemesle, 2009). A semi-discrete model is a hybrid dynamical system that undergoes continuous dynamics in ordinary differential equations (ODE) most of the time and that experiences discrete dynamics, mimicking pathogen overwintering, at some given time instants. Here, the discrete part of the model describes the inter-season harvesting

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and planting dynamics as well as pathogen overwintering while the continuous part describes the in-season epidemic dynamics. The parameters and variables of the model are listed in table 1.

Table 1. List of the parameters and of the state variables of the model.

Parameters	**Designation (unit) (Reference value)**	**Levels[a] (sensitivity analysis)**
Ω_{int}	Epidemic intensity in a landscape sown with only susceptible plants (mean proportion of plant infected along a season) (0.5)	4 levels: 0.1, 0.3, 0.5, 0.8
Ω_{pfl}	Epidemic profiles $\left(\Omega^1_{pfl},\Omega^2_{pfl},1-\Omega^1_{pfl}-\Omega^2_{pfl}\right)$ (for a given Ω_{int}, Ω^1_{pfl} is the relative contribution of the reservoir to the epidemic intensity measured by the AUDPC in a given field, Ω^2_{pfl} the relative contribution of the between field infections and the remaining part $1-\Omega^1_{pfl}-\Omega^2_{pfl}$ the relative contribution of within field infections.) (1/3,1/3,1/3)	10 levels[b]
λ	Characteristic of the viral dynamics in the reservoir (0.5)	3 levels: 0.1, 0.5, 0.9
φ	Cropping ratio (proportion of resistant cultivar in the cultivated compartment)	5 levels: 0.2, 0.4, 0.6, 0.8, 1
θ	Characteristics of the resistance gene (equilibrium frequency of the RB virus in a susceptible plant)	5 levels: 10^{-8}, 10^{-6}, 10^{-4}, 10^{-2}, 0.5
n_y	Number of years of resistance deployment (year) (15)	2 levels: 15, 20
n_d	Duration of the annual cropping season (day) (120)	
n_f	Number of fields in the landscape (fields) (100)	
n_p	Number of plants in a field (plant) (10^4)	
State variables	**Designation (unit)**	
$I_{S,y}$	Number of infected plants in a field sown with the susceptible cultivar during year y (plant)	
$I_{R,y}$	Number of infected plants in a field sown with the resistant cultivar during year y (plant)	
$\bar{\alpha}_{S,y}$	Rate of infection of the susceptible cultivar by reservoir hosts infected with wild-type or RB viruses during year y (t^{-1})	
$\bar{\alpha}_{R,y}$	Rate of infection of the resistant cultivar by reservoir hosts infected with RB viruses during year y (t^{-1})	

[a] Levels combined to derive the full factorial design used to compute sensitivity indices.

[b] Ten epidemic profiles were distinguished: (0.05,0.05,0.9), (0.05,0.9,0.05), (0.9,0.05,0.05), (0.2,0.2,0.6), (0.2,0.6,0.2), (0.6,0.2,0.2), (0.45,0.1,0.45), (0.1,0.45,0.45), (0.45,0.45,0.1) (1/3, 1/3, 1/3).

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Model in a fully susceptible landscape. We first describe the model in a landscape where all fields are sown with the susceptible cultivar (φ=0). Along this study, this case will define baseline epidemiological contexts (along with the parameter λ characterizing the viral reservoir and described thereafter) and, for each epidemiological context, we will investigate how the introduction of a proportion φ>0 of resistant fields impact virus epidemiology. Two classes of plants are considered: healthy and infected. The state variable of interest is $I_{S,y}$ the number of infected plants in a given susceptible field during year y. The size of the host population remains fixed to n_p plants per field. The number of new infections per unit time is determined by the mass action principle between healthy and infected plants which implies random contacts (through insect vectors) between plants. In a given field, each of the $\left(n_p - I_{S,y}\right)$ healthy plants can get the disease from the $I_{S,y}$ plants infected in the same field at a contact rate β_F (unit plant^{-1} t^{-1}) or from the $\left(n_f - 1\right) I_{S,y}$ plants infected in the other fields at a contact rate β_C (unit plant^{-1} t^{-1}). Secondly, they can also get the disease from plants infected in the reservoir compartment. The size of the population of reservoir hosts infected is not explicitly modelled but indirectly taken into account in the rate α_E (unit t^{-1}). The corresponding ODE is:

$$\frac{dI_{S,y}}{dt} = \left(n_p - I_{S,y}\right)\left(\alpha_E + \beta_C\left(n_f - 1\right)I_{S,y} + \beta_F I_{S,y}\right) \quad (1)$$

with $I_{S,y}\left(0\right) = 0$ for $y \in \left[1, n_y\right]$ since, by hypothesis, only healthy plants are sown. In the baseline cases (φ=0), epidemics are repeated each year y with the same dynamics in each field. Integrations of equation 1 define the area under disease progress curve (AUDPC) in a field. AUDPC is a measure of epidemic intensity. At landscape scale, for φ=0, the overall AUDPC is $A_0 = n_f \int_0^{n_d} I_{S,y}(t)dt$.

The epidemic parameters $\left(\alpha_E, \beta_C, \beta_F\right)$ of equation 1 define the intensities of the 3 routes of infection in a landscape sown with only susceptible fields. We reparameterized the epidemiological context with 2 parameters having *a priori* an easier meaningful interpretation, Ω_{int} and Ω_{pfl}. Ω_{int} is the mean incidence (i.e. mean proportion of plants infected along the season) in a landscape composed of n_f susceptible fields sown with n_p plants during n_d days each year. It characterizes the annual epidemic intensity. Note that $A_0 = n_f n_p n_d \Omega_{int}$. $\Omega_{pfl} = \left(\Omega^1_{pfl}, \Omega^2_{pfl}, 1 - \Omega^1_{pfl} - \Omega^2_{pfl}\right)$ characterizes the landscape structure. It defines the relative proportions of the 3 types of infection events leading to a given value of Ω_{int} : Ω^1_{pfl} is the relative contribution of the reservoir to the epidemic intensity measured by the AUDPC in a given field, Ω^2_{pfl} the relative contribution of the between fields infections and the remaining part $1 - \Omega^1_{pfl} - \Omega^2_{pfl}$ the relative contribution of within field infections. Note S1 details the correspondence between $\left(\alpha_E, \beta_C, \beta_F\right)$ and $(\Omega_{int}, \Omega_{pfl})$.

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Introduction of resistant fields into the epidemic model. A new state variable, $I_{R,y}$, the number of infected plants in a resistant field during year y, is used to define the following ODE system:

$$\begin{cases} \dfrac{dI_{S,y}}{dt} = \left(n_p - I_{S,y}\right)\left[\bar{\alpha}_{S,y} + \beta_C\left[\left((1-\varphi)n_f - 1\right)I_{S,y} + \varphi n_f I_{R,y}\right] + \beta_F I_{S,y}\right] & (2) \\ \dfrac{dI_{R,y}}{dt} = \left(n_p - I_{R,y}\right)\left[\bar{\alpha}_{R,y} + \beta_C\left[(1-\varphi)n_f\theta I_{S,y} + \left(\varphi n_f - 1\right)I_{R,y}\right] + \beta_F I_{R,y}\right] & (3) \\ I_{S,y}(0) = I_{R,y}(0) = 0 \quad \text{for} \quad y \in \left[1, n_y\right] \end{cases}$$

Equation 2 is a generalisation of equation 1 to cases where φ>0. The rate α_E is replaced by $\bar{\alpha}_{S,y}$, the rate of infection of a healthy plant (of the S cultivar) in a field during year y by an infected plant of the reservoir. Equation 3 is similar to equation 2 except that: (i) the rate $\bar{\alpha}_{S,y}$ is replaced by the rate $\bar{\alpha}_{R,y}$ of infection of a healthy plant (of the R cultivar) during year y by a reservoir host infected with RB virus and (ii) the rate β_C is discounted by the parameter θ, the frequency at which the RB variant co-exist with the wild-type at equilibrium in a susceptible host. θ depends on the number of mutations required for resistance breakdown and on the associated fitness costs (Fig. 1; Supporting information Note S2). It determines the probability of acquisition of the RB virus in an infected plant of the susceptible cultivar. Integrations over time of equations 2 and 3 provide the AUDPC. $A_{S,y} = (1-\varphi)n_f\int_0^{n_d} I_{S,y}(t)dt$ is the AUDPC in all susceptible fields during year y, $A_{R,y}$ the AUDPC in all resistant fields and $A_y = A_{S,y} + A_{R,y}$ the overall AUPDC in the cultivated compartment.

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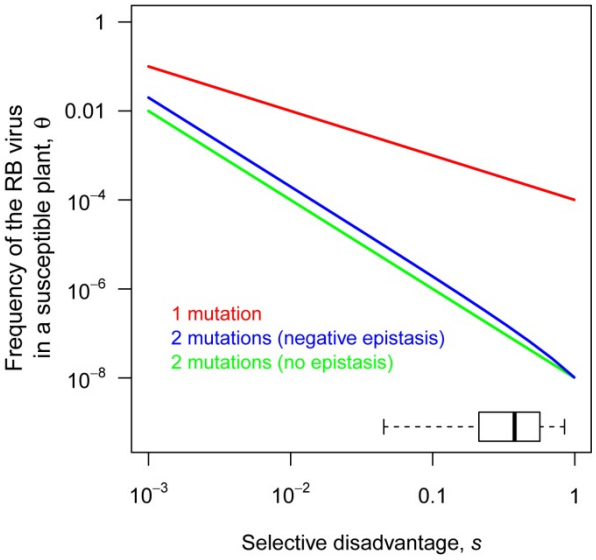

Figure 1. Relationship between the parameter characterizing a resistance gene (θ) and the number and fitness cost of mutations required for resistance breakdown. In a susceptible host, the wild-type and RB virus variants co-exist at an equilibrium frequency (θ) defined by the mutation-selection balance. The values of θ were estimated for 2 determinants of resistance breakdown, requiring 1 or 2 mutations, and for individual fitness cost of mutation (selective disadvantage) ranging from very low (10^{-3}) to high (1) values. Two cases were distinguished when 2 mutations are required for virulence: (i) no epistasis (the 2 mutations have independent fitness effects) and (ii) high negative epistasis (the second mutation had no further fitness effect). Calculations are detailed in supporting information Note S2. The boxplot indicates the probability distribution of non-lethal fitness effects of single mutations as determined by Carrasco *et al.* (2007) on a collection of 66 clones of *Tobacco etch potyvirus* (Beta probability density function with α=1.151 and β=1.709).

Model for the viral load of the reservoir. Modelling the epidemiology of a viral disease of annual crops over several years involves describing virus dynamics in the reservoir. It is assumed that reservoir hosts are selectively neutral for the virus populations: they keep unchanged the relative frequencies of the wild-type and the RB variants issued from the crops (i.e. there is no fitness cost for the RB variant in the reservoir). Nevertheless the prevalence of the virus is changing between seasons according to a parameter λ ($0 < \lambda < 1$). High values of λ characterize rapidly changing reservoir either because of (i) a low mean lifespan of host species (annual species are the main hosts), (ii) a low rate of secondary spread between reservoir hosts (virus prevalence in the reservoir is mainly driven by disease dynamics in the crops) and (iii) a small size of the reservoir host population (virus prevalence in the reservoir can change rapidly). On the opposite, low values of λ characterize a roughly stable reservoir where virus dynamics marginally depends on disease dynamics in the crops. The model is:

An exponential mobile average (equation 4) describes the inter-season dynamics of the rate of infection of the susceptible cultivar from reservoir hosts infected with the wild-type or the RB virus variants ($\bar{\alpha}_{S,y}$). The dynamics of $\bar{\alpha}_{S,y}$ is controlled by two processes: (i) the weight λ that characterizes the rate of renewal of the reservoir (higher λ discounting the impact of older epidemiological dynamics issued from the crops faster) and (ii) the relative overall epidemic intensity observed during year y-1 (the lower the ratio A_{y-1}/A_0 is, the lower the involvement of the crops to maintain virus prevalence in the reservoir compartment). As introducing the resistance can only decrease epidemic intensity, it is clear that $\bar{\alpha}_{S,y} \le \alpha_E$ for $y \in [1, n_y]$. Note also that for φ=0, $\bar{\alpha}_{S,y} = \alpha_E$ for $y \in [1, n_y]$ consistently with equation 1. Equation 5 describes in a similar way the inter-season dynamics of the rate of infection of the resistant cultivar by reservoir hosts infected with RB viruses only ($\bar{\alpha}_{R,y}$) assuming that the susceptible cultivar contributes according to θ, the equilibrium frequency of the RB variant, to the infection of the reservoir hosts.

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$$\begin{cases} \bar{\alpha}_{S,y} = \lambda \dfrac{\alpha_E \left(A_{S,y-1} + A_{R,y-1} \right)}{A_0} + (1-\lambda)\bar{\alpha}_{S,y-1} \quad \text{for } y \in \left[2, n_y \right] \quad (4) \\ \bar{\alpha}_{R,y} = \lambda \dfrac{\alpha_E \left(\theta A_{S,y-1} + A_{R,y-1} \right)}{A_0} + (1-\lambda)\bar{\alpha}_{R,y-1} \quad \text{for } y \in \left[2, n_y \right] \quad (5) \\ \bar{\alpha}_{S,1} = \alpha_E \quad \text{and} \quad \bar{\alpha}_{R,1} = \theta \alpha_E \end{cases}$$

Model analysis

Parameters of interest: farmers leverages of action

The epidemiological context is defined in a fully susceptible landscape by Ω_{int}, the intensity of epidemics and Ω_{pfl}, the relative proportion of 3 types of infection events as well as by the parameter λ that characterizes the viral reservoir. The leverages of action available to a group of farmers to manage the deployment of a resistant cultivar are the following. Farmers can first choose a resistance gene (by choosing a cultivar). The gene is characterized by the parameter θ which depends on the number of mutations required for resistance breakdown and on the fitness cost incurred by these mutations (Fig. 1; Supporting information Note S2). Farmers can also promote landscape planning policies: (i) implementation of a cropping ratio φ and (ii) landscaping the structure of the agroecosystem (modification of Ω_{pfl} and/or λ). Farmers can also use control methods that decrease Ω_{int}. In practice, all control methods (either chemical, cultural or biological) decrease Ω_{int} and can further impact Ω_{pfl} and/or λ. Jones (2006) have listed control measures targeting either the initial source of virus inoculum or the rate of virus spread by interfering with the population dynamics of insect vectors. For example, the release of biological control agents (e.g. predators, parasites) to control vectors by decreasing the rate of virus spread will likely impact Ω_{pfl}. Push-pull strategies maintaining vectors far from the target crop, habitat management enhancing biological agents or the use of mulches preventing vector landing will do the same. Other methods that aim to decrease the initial source of inoculum will modify λ and/or Ω_{pfl}: removing reservoir hosts (weeds or volunteer plants within and outside fields), deploying non-host barrier crop where incoming vectors lose non-persistently transmitted viruses, using large fields with small perimeter to area ratios. Finally, the number of years of deployment of the resistance (n_y) was included in the analysis although this parameter is only partially dependent on farmers own choices (the lifespan of a cultivar mainly depends on the evolution of consumer preferences as well as on the time needed by plant breeders to release new cultivars).

Model output of agricultural interest: yield improvement

We assumed that yield drives the technical choices of farmers and that AUDPC is a proxy of the yield losses caused by a pathogen (Jeger, 2004). Alternative measures of yield based on Healthy leaf Area Duration (HAD), as used by van den Bosch & Gilligan (2003), are equivalent to AUDPC-based measures when assuming that the leaf area index of the crop is constant (Waggoner & Berger, 1987). Two model outputs of interest were defined:

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(i) $D(\delta,\varphi)$ measures the reduction of the damage (yield losses) done by the pathogen during n_y seasons for a given set of model parameters $\delta = (\theta, \Omega_{int}, \Omega_{pfl}, \lambda, n_y)$ when deploying a proportion φ of resistant cultivar relatively to the damage caused by the pathogen when only the susceptible cultivar is grown in the landscape. $D(\delta,\varphi) = \sum_{y=1}^{n_y} A_y(\delta,\varphi) \Big/ \left(n_y A_0\right)$ (6). For example, a value of $D(\delta,\varphi)$=0.8 means that introducing a resistant cultivar at a cropping ratio φ reduces by 20% the yield losses due to the pathogen compared to a landscape where only a susceptible cultivar is sown. Thereafter $D(\delta,\varphi)$ is called "relative damage".

(ii) $\Phi_{opt}(\delta)$ is the optimal cropping ratio, that is the value of φ minimising $D(\delta,\varphi)$.

Global sensitivity analysis: relative importance of farmers' leverages

Global sensitivity analyses (Saltelli *et al*., 2008) quantify the relative importance of model parameters by partitioning the variance of output variables into those due to the main effects of parameters and their higher order interactions. The sensitivity of $D(\delta,\varphi)$ to the 6 parameters $\theta, \Omega_{int}, \Omega_{pfl}, \lambda, n_y$ and φ was studied. First, a range of variation accounting for the known biological variability ($\theta, \Omega_{int}, n_y, \varphi$) or for a wide range of the possible natural state (Ω_{pfl}, λ) was assigned to each parameter (Table 1). The range of θ accounts for resistance genes requiring the accumulation of 1 or 2 nucleotide substitution(s) to be broken down with very low to high fitness cost (Fig. 1, Note S2). The range of λ accounts for a wide range of the possible state of the reservoir compartment with viral populations having a half-life in the reservoir from ≈ 6 months (λ=0.9) to ≈ 6 years (λ=0.1). Second, levels spaced in these ranges were defined (Table 1) and the model was run for the 7200 parameter combinations of the corresponding full factorial design. Third, sensitivity indices were estimated from the simulation results as the part of variance explained by a factor alone (main effects) or by its 2- or 3-order interactions relative to the total variance by fitting an ANOVA linear model including 3-order interactions to the data generated by simulation. As this ANOVA linear model fit very well (99% of variance explained), sensitivity indices could be derived properly. Sensitivity indices of the mean values of $\Phi_{opt}(\delta)$ to the 5 parameters $\theta, \Omega_{int}, \Omega_{pfl}, \lambda$ and n_y were assessed similarly. The parameters n_f, n_p and n_d were not included in the sensitivity analyses. Indeed, as Ω_{int} and Ω_{pfl} are defined given n_f, n_p and n_d, $D(\delta,\varphi)$ is independent of their values. Global sensitivity analyses were combined with graphical analyses where parameters vary one-at-a-time to investigate how they individually impact the output variables of interest. The model and analyses were implemented with the R software environment (http://www.r-project.org/) using the library "deSolve".

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Results

Overview of model dynamics

An example of dynamics simulated by the model is provided in figure 2. The epidemiological context is defined by intermediates epidemic profile (Ω_{pfl}=(1/3,1/3,1/3)), epidemic incidence (Ω_{int}=0.5) and rate of reservoir change (λ=0.5). Each year *y*, when the landscape is sown with only the susceptible cultivar, the same epidemic occurs in the fields (Fig. 2a-c, φ=0, blue lines). The rate of infection from the reservoir is thus constant (Fig. 2d, $\bar{\alpha}_{S,y} = \alpha_E$) as well as the relative annual yield losses equal to 1, by definition (Fig. 2e, A_y/A_0). This is the baseline epidemiological situation. Now, let deploy the resistant cultivar in 80% of the fields. During the first year, as the frequency of the RB virus in the reservoir is low, very few resistant plants are infected (Fig. 2b, red lines) whereas epidemics spread in the susceptible cultivar although with a lesser intensity due to fewer between-field infection events (Fig. 2a, red lines). The relative annual yield drops to $A_1/A_0 \approx 0.2$ (Fig. 2e) and, consequently, the rate of infection between infected reservoir hosts and the susceptible cultivar ($\bar{\alpha}_{S,2}$) is decreased (Fig. 2d). This process slows down epidemics in the susceptible fields during the first years (Fig. 2a). However, at the same time, this process is counteracted by the increasing number of resistant plants infected (which cover 80% of the cultivated compartment) and thus by the increase of the rate of infection of the resistant cultivar by reservoir hosts infected with RB viruses (Fig. 2d, $\bar{\alpha}_{R,y}$). Overall, the fast resistance breakdown observed (Fig. 2c, red lines) leads to a rapid increase of the relative annual yield losses over years although they do not return to 1 (Fig. 2e).

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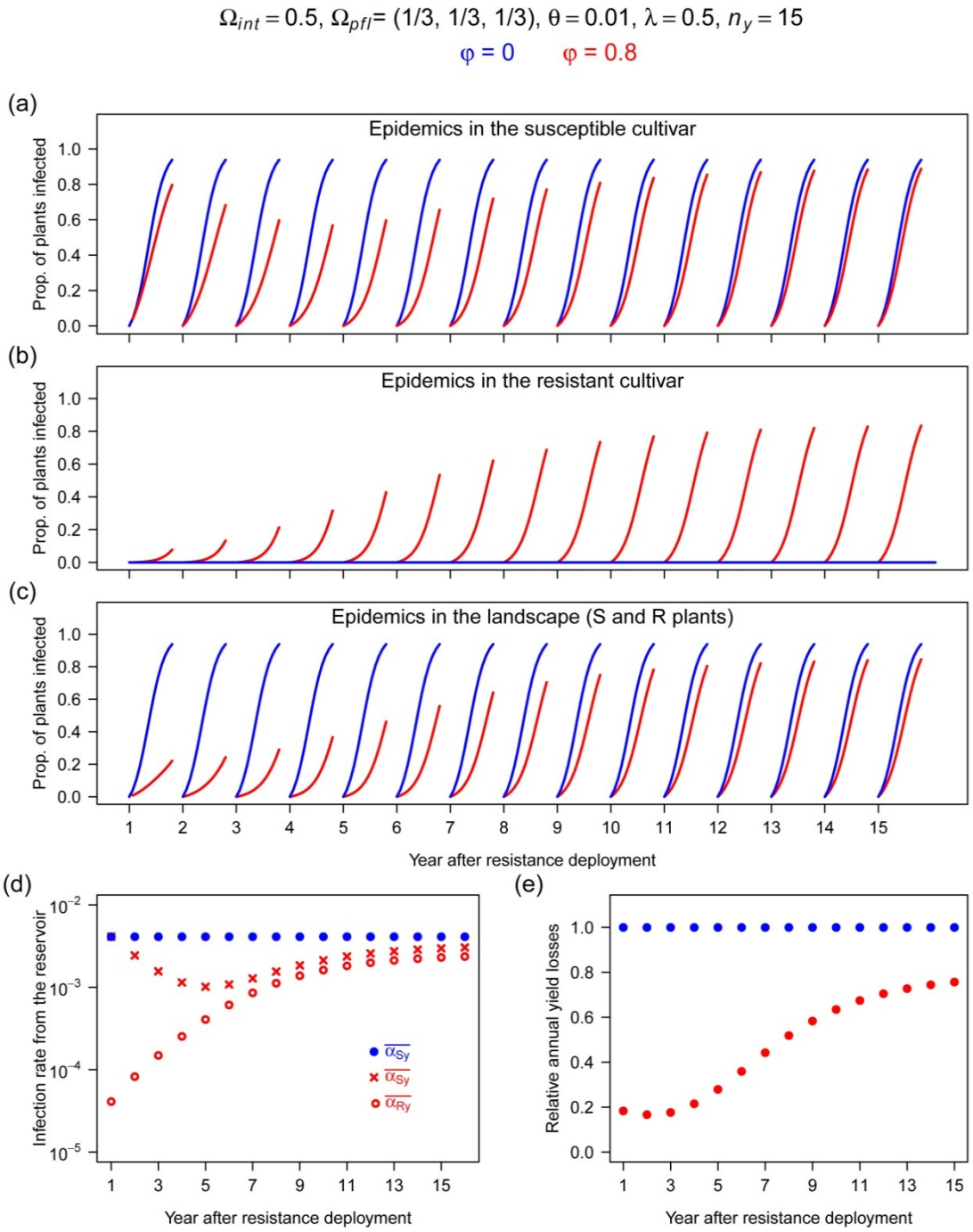

Figure 2. Typical epidemics simulated by the model at landscape scale. Epidemic dynamics are compared between a baseline situation (φ=0), where only the susceptible cultivar is cultivated, and a situation where 80% of the fields are cultivated with the resistant cultivar (φ=0.8). The baseline epidemiological context of the simulation is defined by intermediate values (Ω_{pfl}=(1/3,1/3,1/3)), Ω_{int}=0.5 and λ=0.5). The resistance gene is characterized by θ=0.01. **(a)**: Proportion of susceptible plants infected ($I_{S,y}/n_p$) during 15 cropping seasons simulated. **(b):** Proportion of resistant plants infected ($I_{R,y}/n_p$). **(c):** Proportion of plants of both cultivars infected ($\left(n_f^S I_{S,y} + n_f^R I_{R,y}\right)/\left(n_f n_p\right)$). **(d)**: Inter-seasons dynamics of the rate of infection of the susceptible cultivar by reservoir hosts infected with wild-type or RB viruses ($\bar{\alpha}_{S,y}$) and of the resistant cultivar by reservoir hosts infected with RB viruses ($\bar{\alpha}_{R,y}$). **(e)**: Inter-season dynamics of the relative annual yield losses (A_y/A_0). Other parameters were set to their reference values (Table 1).

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Analysis of relative damage

Relative importance of farmers' leverages. Sensitivity analyses indicate that the mean epidemic incidence (Ω_{int}) was the most influential factor of the relative damage D (45% of the variance, Fig. 3a). The next factor, the characteristic of the R gene (θ) alone accounting for 24% of the variance, is followed by the cropping ratio (φ) and the epidemic profile (Ω_{pfl}) (8 and 4% of explained variance). In all, the main effects of these 4 factors explained 80% of the variance of D (Fig. 3a). In decreasing importance, the next sensitivity indices are mostly the 2-order interactions between these 4 parameters (12% of the remaining variance). Conversely, the characteristic of the viral dynamics in the reservoir (λ) and the number of years of R deployment (n_y) were negligible on their own (< 0.1%). Significant interactions were however detected between λ and φ and λ and Ω_{int} (4% of the variance of D in total).

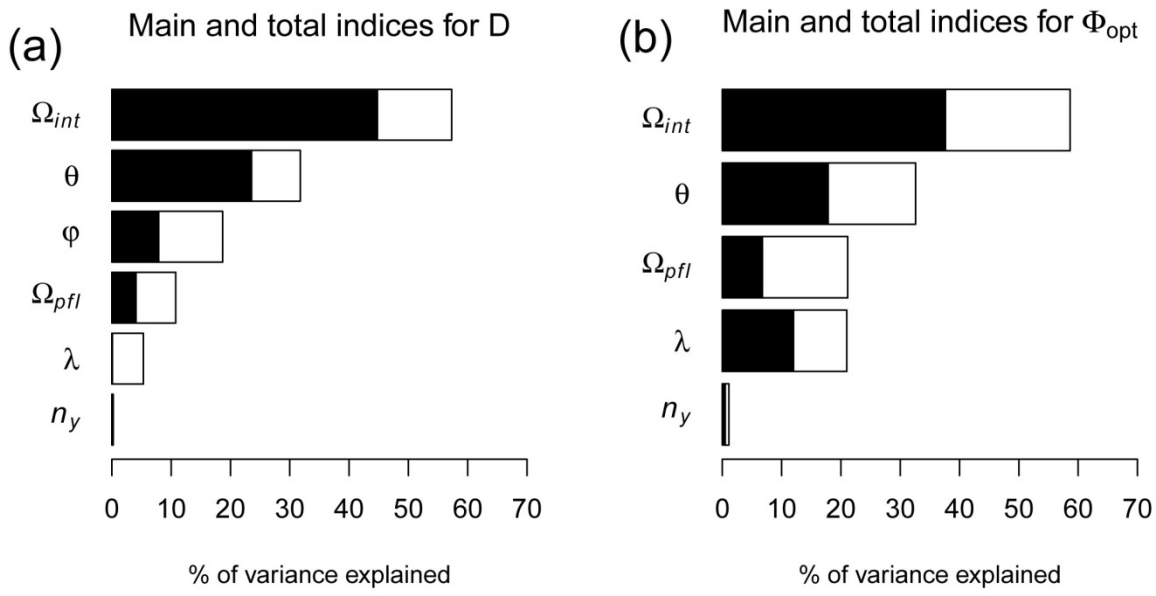

Figure 3. Sensitivity indices of the relative damage (D) and of the optimal cropping ratio (Φ_{opt}). The effect of six factors is analysed for D: θ: characteristic of the resistance gene, λ: characteristic of the viral dynamic in the reservoir, Ω_{int}: epidemic intensity, Ω_{pfl}: epidemic profile, n_y: number of year of deployment of the resistance and φ: the cropping ratio. Only the first five factors are analysed for Φ_{opt}. **(a)**: Main and total sensitivity indices for D. **(b)**: Main and total sensitivity indices for Φ_{opt}. The black parts of bars correspond to main indices (effect of the factor alone) and full bars (black and white parts) correspond to total indices (white parts correspond to the effect of the factor in interaction with all others factors).

Individual effect of farmers' leverages. One-at-a-time analyses were used to decipher the effects on damage of the most important factors revealed by sensitivity analysis. D was plotted as a function of the cropping ratio (φ) according to 5 values of θ ranging from 10^{-8} to 0.5. The value θ=0.5 corresponds to a resistance requiring 1 mutation with no fitness cost to be broken down while θ=10^{-8} corresponds to a resistance requiring 2 mutations with a high fitness cost (Fig. 1). In all graphs, the dotted line, simulated by setting θ to 0, indicates the level of relative damage obtained when deploying a resistance impossible to breakdown. The grey area below this dotted line defines unreachable levels of relative damage. As soon as curves characterized by $\theta > 0$ do not fit the dotted line, there are cases of breakdown. The yield losses due to these breakdowns remain lower than the

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yield benefits obtained by deploying the resistance (by slowing down epidemics in susceptible fields) if the curve is located below the diagonal line.

The effect of Ω_{int}, the most important factor according to sensitivity analysis, on relative damage (D) is illustrated in figure 4 (Fig. 4a-c). In landscapes with low epidemic incidence (Fig. 4a, Ω_{int} = 0.1), the curves $D=f(\varphi)$ fit the dotted curve for resistance genes characterized by $\theta \leq 0.01$ revealing that resistances are not broken down whatever the cropping ratio. Also, they are markedly located below the diagonal revealing that the deployment of the resistance slows the epidemics down in the susceptible fields (due to lower rates of infection between reservoir and fields as well as between fields). Only the curve $D=f(\varphi)$ for θ=0.5, which characterises a resistance requiring 1 mutation with no fitness cost to be broken down, exhibits a parabolic shape with a minimum of damage near φ = 0.6. These parabolic-shaped curves are the rule for most resistance genes ($\theta \in [10^{-6}, 0.5]$) in landscapes with intermediate epidemic incidence (Fig. 4b, Ω_{int} = 0.5). They indicate that resistance genes are broken down above some threshold value of φ where curves move away from the dotted line. The lower θ is, the higher this threshold. They also show that the damages are minimized for a cropping ratio somewhat higher than this threshold and then increase again without coming back to their baseline value 1. In this landscape, only the resistance gene characterized by the lowest value of θ (10^{-8}) is never broken down. Finally, in landscapes with high epidemic incidence (Fig. 4c, Ω_{int} = 0.8), resistance genes are most often broken down and yield loss reduction is low (<20%). The curves $D=f(\varphi)$ first fit the dotted line, which is very close from the diagonal, for low cropping ratio (φ<0.2), revealing the absence of resistance breakdown and of slowing down of epidemics in susceptible fields, and then, for higher cropping ratio, they rapidly level off.

The effect of the epidemic profile Ω_{pfl} on D is elucidated for a given Ω_{int} by comparing 3 profiles (Fig. 4 d-f) to the reference Ω_{pfl} =(1/3,1/3,1/3) (Fig. 4b). The profile where 90% of the infection events are "primary infections from the reservoir" (Fig. 4d: Ω_{pfl} = (0.9,0.05,0.05)) is the one that best prevent resistance breakdown while drastically decreasing damage. In particular, resistance genes characterized by θ=10^{-4} or 10^{-6}, that were broken down for cropping ratio > 0.7 under the reference Ω_{pfl} =(1/3,1/3,1/3) (Fig. 4b), are no more overcome since their relative damage curve coincide with the dotted line. The case of the second profile (Fig. 4e: Ω_{pfl} = (0.05,0.9,0.05)) where 90% of the infection events are "primary infections between fields" is more complex. On one hand, compared to the reference profile (Fig. 4b), it favours the damage reduction obtained with resistance genes characterised by intermediate values of θ (10^{-2} to 10^{-6}). On the other hand, it favours the breakdown of the resistance gene characterized by lower θ (10^{-8}). On the opposite, the third profile (Fig. 4f: Ω_{pfl} = (0.05,0.05,0.9)) where infection events are dominated by "secondary infections within individual fields" displays a very different, and much less desirable, situation. Even the resistance gene characterized by θ=10^{-8} that was never overcome in the reference scenario, is here broken down for as low cropping ratios as φ =0.2. Moreover, damages are at best reduced by 45%, whatever the resistance gene and cropping ratio considered, which is a very weak performance compared to the other situations (Fig. 4b,d-e). Actually, similar effects are obtained when epidemic intensity increases from intermediate (Ω_{int} = 0.5) to high (Ω_{int} = 0.8) levels (Fig. 4 b,c).

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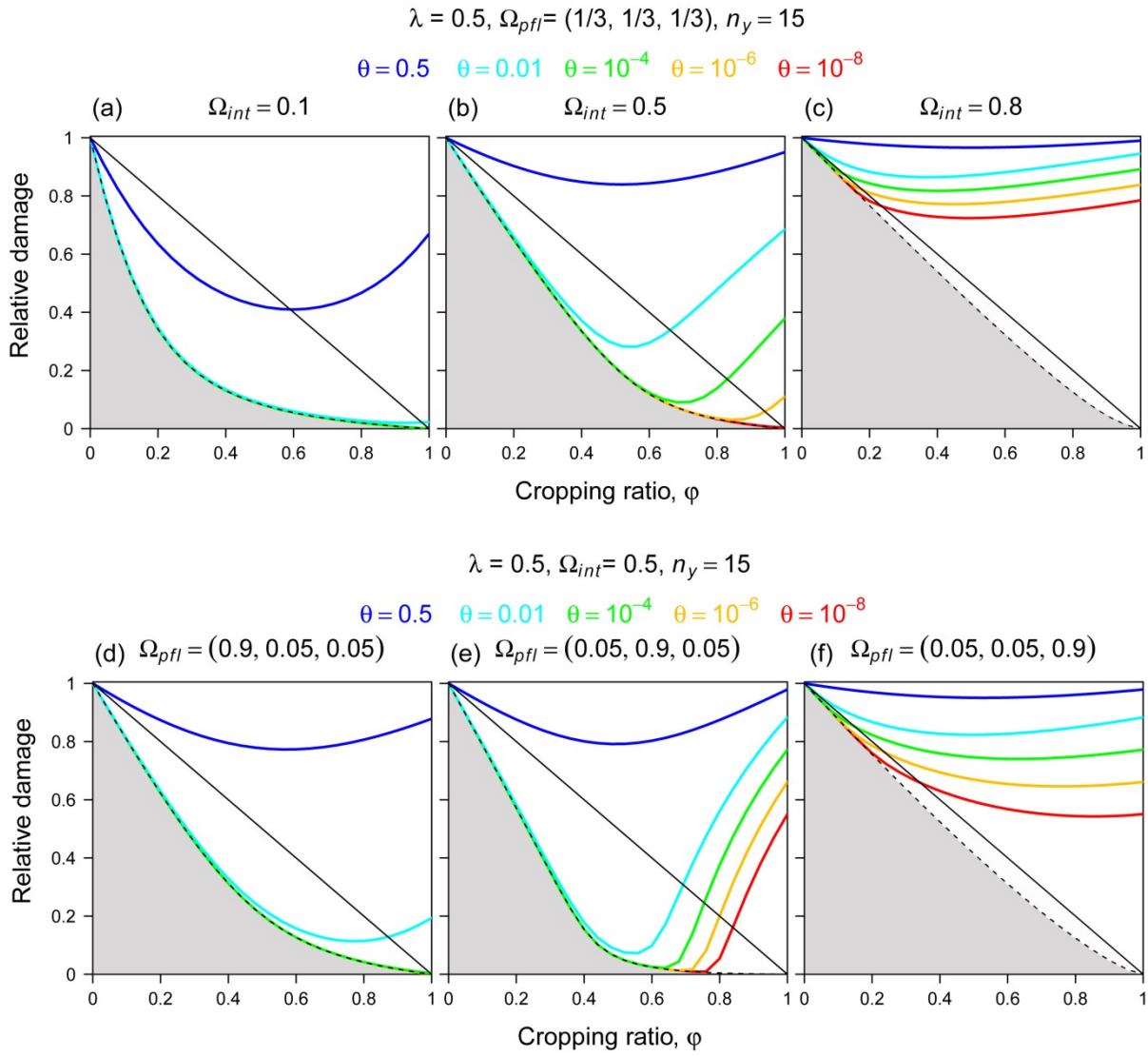

Figure 4. Effects of the intensity of epidemic (Ω_{int}) and of the epidemic profile (Ω_{pfl}) on the relative damage (D). Plots **(a)** to **(c)**: effect of 3 increasing values of Ω_{int}. Plots **(d)** to **(f)**: effect of 3 values of Ω_{pfl}. In each plot, D is plotted as a function of the cropping ratio φ for 5 values of the characteristics of the resistance gene θ. Other parameters were set to their reference values (Table 1). In all graphs, the dotted line corresponds to a resistance impossible to break down (simulated by setting θ to 0). The grey area below this dotted line defines unreachable levels of relative damage. When hidden, curves are under the dotted line.

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Analysis of the optimal cropping ratio.

The optimal cropping ratio, Φ_{opt}, is mainly sensitive to Ω_{int} (main effect 38%) and secondarily to the 3 parameters θ (18%), λ (12%) and Ω_{pfl} (7%) (Fig. 3b). Altogether these 4 parameters explain alone 75% of the variance of Φ_{opt} and 99% when adding their mutual interactions. Conversely, the effect of the number of years of R deployment (n_y) is negligible (<0.5%). The most important interactions were interactions between θ and Ω_{int} (6.5%) and Ω_{pfl} and Ω_{int} (6.5%).

Φ_{opt} was plotted as a function of Ω_{int} for 5 characteristics of the resistance gene (θ), 4 of epidemic profiles (Ω_{pfl}) and 3 characteristic of the viral reservoir (λ) (Fig. 5). The optimal deployment strategies of resistance gene requiring 1 mutation with no fitness cost to be broken down (θ=0.5) are remarkably stable, ranging from 0.7 to 0.5 depending on Ω_{pfl} and λ (Fig. 5 a-f). On the opposite, the optimal deployment strategies of resistance with lower θ ($\leq$0.01) are more variable. A general trend is however observed for 3 epidemic profiles (Fig. 5 a-e - Ω_{pfl} =(1/3,1/3,1/3), (0.9,0.05,0.05) and (0.05,0.9,0.05)). A pure strategy (with only the resistant cultivar) is optimal below a threshold value of epidemic intensity (Ω_{int}^{C}). Ω_{int}^{C} increases (i) when the frequency of the RB virus in a susceptible host plant (θ) decreases and (ii) when the proportion of infection events originated from the reservoir increases (Fig. 5d, Ω_{pfl} =(0.9,0.05,0.05)). Above Ω_{int}^{C}, Φ_{opt} is decreasing roughly linearly with Ω_{int}. The optimal strategy is to deploy a mixture of cultivars where, most of the time, the resistant cultivar is in higher proportion than the susceptible one.

A different picture is obtained when secondary infections within fields dominate infection events (Fig. 5f: Ω_{pfl} = (0.05,0.05,0.9)). A bell-shaped curve characterizes the lowest value of θ (10^{-8}), pure strategies with only resistant fields being optimal both for low ($\leq$ 0.3) and high ($\geq$ 0.6) epidemic intensities. This curve transforms when θ increases: (i) on one hand, pure strategies become restricted to the lowest epidemic intensities (θ=10^{-6} and 10^{-4}), (ii) on the other hand, there is a threshold of Ω_{int} above which the optimal strategies become fairly independent on epidemic intensities (θ=10^{-4} and 10^{-2}).

Finally, optimal strategies were nearly identical for reservoir compartment responding averagely (Fig. 5b, λ=0.5) or rapidly (Fig. 5c, λ=0.9) to viral dynamics in the crops. Some differences were observed in landscapes with slowly changing reservoirs (Fig. 5a, λ=0.1) that always favour higher cropping ratios.

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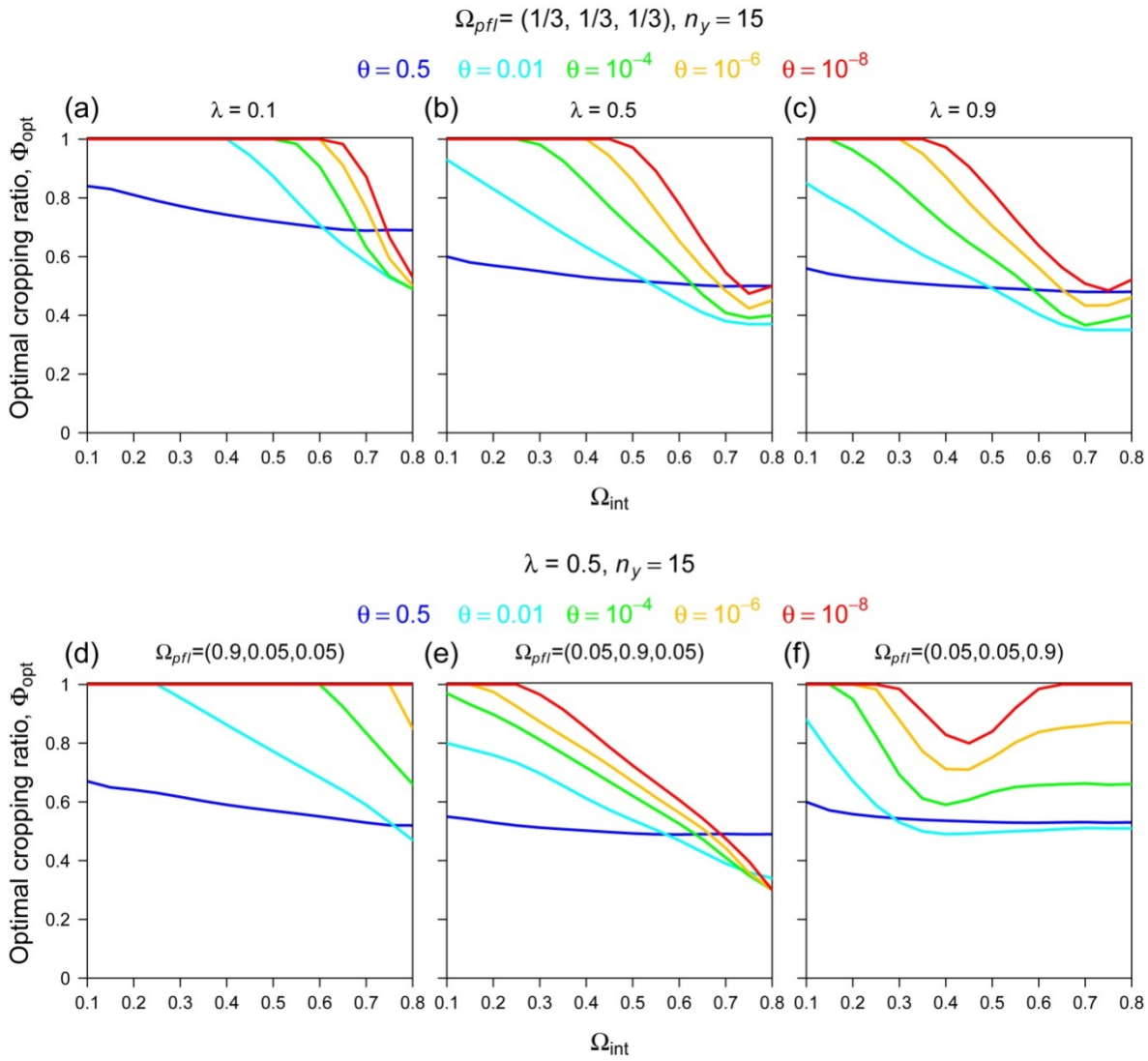

Figure 5. Effects of the intensity of epidemic (Ω_{int}), of the profile of epidemic (Ω_{pfl}) and of the characteristic of the viral dynamic in the reservoir (λ) on the optimal cropping ratio (Φ_{opt}). Plots **(a)** to **(f)**: effects of 6 combinations of the parameters Ω_{pfl} and λ. In each plot, Φ_{opt} is plotted as a function of epidemic intensity Ω_{int} for 5 values of the characteristics of the resistance gene θ. Other parameters were set to their reference values (Table 1).

Discussion

Major determinants of the relative damage. Van den Bosch & Gilligan (2003) were pioneering in measuring durability by the additional yield provided by resistance deployment. This is a proxy of the accumulated profit obtained by releasing a resistant cultivar. Assuming no fitness cost for resistance breakdown, they demonstrated, for a foliar pathogen in a system with continuous planting and harvesting, that the additional yield was only slightly dependent on the cropping ratio. The present study shows that the very same result holds for systemic pathogens like viruses as long as the epidemic intensity Ω_{int} is large (Fig. 4c). However, as epidemic intensity becomes milder, the relative damage (D) becomes much more sensitive to the cropping ratio φ (Fig. 4a,b). Actually, for high epidemic intensities, all plants become infected very rapidly during the cropping season. Since

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D is computed from the AUDPC, the time period during which all plants are infected has a lot of weight in the value of *D*: long periods tend to level out the effects of the other parameters. This explains the somewhat counter-intuitive result that Ω_{int} is the main driver of *D* variance (Fig. 3a) even though *D* is computed relatively to the overall epidemic intensity in a landscape with only susceptible plants (equation 6).

The second most important factor explaining *D* variance is the characteristic of the resistance gene θ. Practically, in landscapes with low to intermediate epidemic intensities (Fig. 4a,b: $\Omega_{int} \leq 0.5$), resistance genes characterized by $\theta \leq 10^{-6}$ are likely to be durable, whatever the cropping ratio adopted. Values of $\theta \leq 10^{-6}$ typically correspond to resistances defeated by two mutations, each non-lethal individual mutation reducing virus fitness by 10-13% on average (Sanjuán, 2010; Fig. 1). The deployment of such resistance genes significantly reduces the relative damage, often by a factor higher than the proportion of resistance released. However, resistance genes defeated by a single mutation characterized by $\theta \in [10^{-4}, 10^{-2}]$ can only be durable in landscapes with low epidemic intensities (Fig. 4a: $\Omega_{int} = 0.1$).

These results are consistent with the observed increase of resistance durability with the number of mutations needed for resistance breakdown (Harrison, 2002; Lecoq *et al.*, 2004) as well as with theoretical studies (Fabre *et al.*, 2009). They are also consistent with the hypothesis, recently demonstrated for plant viruses (Janzac *et al.*, 2009, 2010; Fraile *et al.*, 2011), that resistance genes imposing a high penalty to the pathogen for adaptation will likely be durable (Leach *et al.*, 2001). For farmers, the choice of the resistance gene is a very influential leverage of action even if no resistance was proved to be durable in landscapes with high epidemic intensities. In these latter scenarios, whatever the resistance gene and the cropping ratio used, yield losses are at most reduced by 30% and often only by 15-20% (Fig. 4c). In practice, the falling costs of high-throughput sequencing techniques (Brockhurst *et al.*, 2011) now allow to check if virus populations are at the mutation-selection equilibrium and allow to provide an estimate of θ *in planta* that take into account the possible effects of recombination or compensatory mutations on fitness cost recovery (Torres-Barcelo *et al.*, 2009; Janzac *et al.*, 2010). These techniques could also be used to investigate the pace at which virus populations approach the within-host selection-mutation equilibrium. We assumed here that this occurs instantaneously compared with the epidemiological time scale. This hypothesis is all the more likely that (i) the mean effect of deleterious mutations is high (which is indeed the case for RNA viruses) and (ii) the variance of the mutational effect is low (T. Johnson, 1999).

Optimal strategies of resistance deployment. No universal strategy exists. Overall, two broad categories were highlighted: "mixture" and "purely resistant" strategies. Strategies that mix susceptible and resistant cultivars are optimal when resistance breakdown occurs rapidly. Firstly, whatever the resistance gene considered, mixture strategies are optimal in landscapes with high epidemic intensities (Fig. 5a, $\Omega_{int} \geq 0.5$). Such strategies actually make a compromise between (i) maximizing yield (the higher the cropping ratio, the higher the contribution of the resistance to the overall yield) and (ii) minimizing the probability of resistance breakdown (the lower the cropping ratio, the lower the selection exerted by the crops on the RB variant). Secondly, for any epidemic intensity, mixture strategies are optimal for low fitness costs of resistance breakdown (Fig. 5a: $\theta \geq 0.01$), when the equilibrium frequency of the RB variant in susceptible hosts is high (Fig. 1). By modelling gene-for-gene interactions between crop plants and a fungi-like pathogen during a single season, Ohtsuki & Sasaki (2006) also demonstrated that, with no fitness costs, intermediate cropping ratios are optimal.

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In sharp contrast to the conventional approach (releasing resistance genes at low cropping ratio, Pink & Puddephat, 1999), pure strategies with up to 100% of resistant cultivar can also be optimal. This arises first when the pathogen population is unlikely to be invaded by the RB variant, typically when 2 mutations with average fitness costs (for RNA viruses) are required for resistance breakdown in landscapes with intermediate, or lower, epidemic intensities (Fig. 5a: $\theta \leq 10^{-4}$ and $\Omega_{int} \leq 0.5$). This also arises in landscapes where epidemics are primarily driven by infections from the reservoir (Fig. 5d) because the reservoir initially hosts very few RB variants, causing little infections of resistant plants which in turn fail to efficiently infect the reservoir back (equation 5). Finally, pure resistant strategies are also relevant in landscapes with low removal rates in the reservoir, so that the viral dynamics in the reservoir responds slowly to the selection pressure exerted by the resistant cultivar. With different hypotheses (e.g. durability measured by the time until invasion of the RB pathogen, without immigration), van den Bosch & Gilligan (2003) also demonstrated the value of high cropping ratios.

As a first step, we discuss here deployment strategies remaining constant between seasons over the landscape. These strategies can firstly be improved regarding their time component, by varying the cropping ratio from one season to another, a strategy ever known to reduce the invasion of pesticide resistant pathogens (Hall *et al.*, 2004). They can secondly be improved regarding their space component, by managing the spatial structure of host populations which also impacts pathogen invasions (Gilligan and van den Bosch, 2008) and thus resistance durability (Sapoukhina *et al.*, 2009).

The role of landscape epidemiology for managing durability. The scale of deployment of any control strategy must match the scale where epidemics naturally occur (Dybiec *et al.*, 2004; Gilligan, 2008). In animal and human disease epidemiology, control measures are commonly deployed at large geographical scales (e.g. Ferguson *et al.*, 2001, 2005), but in plant disease epidemiology, control measures at scales larger than fields remain scarce despite their potential interest (Mundt, 2002; Parnell *et al.*, 2006; Gilligan *et al.*, 2007; Plantegenest *et al.*, 2007; Parnell *et al.*, 2009). Beside the effect of resistance deployment at the landscape scale, our model describes the connectivity between the fields and the resevroir of the landscape with the parameter Ω_{pfl}. The search for optimal deployment strategies evidenced its importance: mixture strategies were promoted by high proportions of between-fields infection events (Fig. 5e), while pure resistant strategies were promoted by a high proportion of infections from the reservoir (Fig. 5d). An epidemic with a high frequency of primary infection from the reservoir describes a situation of pathogen spillover (Daszak *et al.*, 2000) where epidemics are primarily driven by transmission from the reservoir hosts. According to our hypotheses, this is the best situation for managing durability (Fig. 4d) because, by releasing the resistance at high cropping ratios, it is almost possible to suppress the virus from the reservoir (see "optimal strategies of resistance deployment"). Exhausting the viral reservoir is not the only way to slow down epidemics. Landscape planning policies increasing the proportion of between-field infections events (i.e. the connectivity between fields), while maintaining intermediate cropping ratios, do the same. Indeed, facilitating field to field dissemination implies that a growing part of RB infections originating from the resistant fields will occur in susceptible fields in which the RB variants are counter-selected. In turn, the susceptible fields initiate infections that are mostly of the wild-type and thus unable to contaminate resistant plants. Overall, this process diminishes the number of effective infections and slows disease spread. Such a mechanism is comparable to the "dilution of inoculum" effect that reduces disease severity in cultivar mixtures (Mundt, 2002). Yet, this result is fairly conditional to the

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system studied since, on the contrary, some authors have shown that higher pathogen dissemination rates can favour resistance of pathogen to fungicide (e.g. Parnell *et al.* 2006).
Understanding how landscape structures (e.g. hedgerows, fragmentation) impact landscape connectivity and the dispersal of insect pest species (vectoring or not viruses), is an active area of research with still few, but interesting, results (Plantegenest *et al*., 2007). For example, Power & Mitchell (2004) and Borer *et al*. (2009) demonstrated how landscape planning policies can manipulate the host community structure of a plant virus to control spillover. The contrasted management strategies advised according to epidemic profiles or reservoir characteristics illustrate the relevance of promoting researches at the agro-ecological interface (Burdon & Thrall, 2008; Jones, 2009).

Conclusion. During the last decades, much effort has been dedicated to understand the mechanisms involved in emergence of RB pathogens. However, much remains to be done to transfer this knowledge to end-users. With this view, as the mid-term financial interest is often a key determinant to adopt innovations, we measure resistance durability by the yield increase obtained by deploying a resistant cultivar. A further step will be to derive management strategies preserving crop yield while maintaining in the long term the efficiency of resistance genes that are also a natural exhaustible resource.

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Supporting information. Brief listing.

Note S1: Derivation of the epidemic rate parameters α_E, β_C and β_F as a function of Ω_{int} and Ω_{pfl}

The epidemic rate parameters $(\alpha_E, \beta_C, \beta_F)$ introduced in equation 1 define the intensities of the 3 routes of infection (between the reservoir and crops, between fields and within field). However, the model was reparameterized with 2 parameters having *a priori* an easier meaningful interpretation, Ω_{int} and Ω_{pfl}. They are defined in a landscape sown with n_f susceptible fields, each with n_p plants and where epidemics run during n_d days each year, so that equation 1 models the landscape epidemics.

Ω_{int} characterizes epidemic intensity in a susceptible field (located itself in a landscape with only susceptible fields) during an annual epidemic by its mean incidence, i.e. the mean proportion of plants infected along the season. Defining the AUDPC in a given field by $\mathrm{A} = \int_0^{n_d} I_{S,y}(t)dt$, we have

$$\Omega_{\mathrm{int}} = \mathrm{A} \Big/ \left(n_p n_d\right) \qquad (7),$$

so that Ω_{int} lies between 0 and 1, with $\Omega_{int} = 0$ when no plants are infected along the season and $\Omega_{int} = 1$ when all the plants are infected from the beginning of the season.

$\Omega_{pfl} = \left(\Omega^1_{pfl}, \Omega^2_{pfl}, 1 - \Omega^1_{pfl} - \Omega^2_{pfl}\right)$ characterizes the landscape structure. It defines the relative proportions of the 3 types of infection events leading to a given value of Ω_{int}: Ω^1_{pfl} is the relative contribution of the reservoir to the epidemic intensity measured by the AUDPC in a given field, Ω^2_{pfl} the relative contribution of the between fields infections and the remaining part $1 - \Omega^1_{pfl} - \Omega^2_{pfl}$ the relative contribution of within field infections.

To derive Ω^1_{pfl} we first compute the number of hosts infected by the reservoir at time t within year y. We get, according to equation 1, $I^1_{S,y}(t) = \int_0^t \alpha_E (n_p - I_{S,y}(\tau))d\tau$. Thus the proportion of the AUDPC contributed by the reservoir in a given field is:

$$\Omega^1_{pfl} = \frac{1}{\mathrm{A}} \int_0^{n_d} I^1_{S,y}(t)dt = \frac{1}{\mathrm{A}} \int_0^{n_d} \left[\int_0^t \alpha_E (n_p - I_{S,y}(\tau))d\tau \right] dt \qquad (8)$$

Similarly, we get :

$$\Omega^2_{pfl} = \frac{1}{\mathrm{A}} \int_0^{n_d} \left[\int_0^t \beta_C \left(n_f - 1\right)\left(n_p - I_{S,y}(\tau)\right) I_{S,y}(\tau)d\tau \right] dt \qquad (9)$$

For each set of values of Ω_{int} and Ω_{pfl} used in the study (Table 1), the corresponding values of $(\alpha_E, \beta_C, \beta_F)$ were determined by optimization with R software environment (http://www.r-project.org/) using the function nlminb for solving the set of equations (7) to (9).

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Note S2: Relationship between the parameter characterizing a resistance gene (θ) and the number and fitness cost of mutations required for resistance breakdown.

The parameter θ is defined as the frequency at which the RB variant co-exists with the wild-type at equilibrium in a susceptible host. The relationships between θ and the number and fitness cost of mutations required for resistance breakdown were established following Ribeiro *et al.* (1998). Using a quasispecies equation, these authors calculate the expected equilibrium frequency of a virus mutant of interest and show how the frequency depends on the number of point mutations between wild-type and mutant virus, the selective disadvantage of the mutant of interest and the intermediate mutants, and the mutation rate. It is equivalent to the equilibrium at mutation-selection balance defined in population genetics (Wikle, 2005).

Ribeiro *et al.* (1998) first show that at equilibrium, the ratio of mutant to wild-type virus differing by only a single point mutation is μ/s where μ is the mutation rate and s is the relative fitness cost of the mutant (selective disadvantage). Note that this is also the approximation of the equilibrium frequency in mutation-selection balance in haploids. We apply the formula to assess the values of θ when the wild-type variant must acquire 1 mutation to break the resistance down for s varying from very low (10^{-3}) to large (1) selective disadvantage and $\mu=10^{-4}$ (Elena *et al.*, 2011).

They calculate next the equilibrium of a virus mutant differing by two point mutations. Four variants are then considered: the wild-type variant (00), the RB variant (11) and two 1-point mutants (01 and 10). Let μ_1 (resp. μ_2) be the mutation rate for the first (resp. second) position and s_{01} (resp. s_{10} and s_{11}) be the selective disadvantage of the variant 01 (resp. 10 and 11). The ratio of the double mutant to wild-type virus is then approximately $(\mu_1\mu_2/s_{11})(1/s_{01}+1/s_{10}-1)$. Assuming that (i) $\mu_1 = \mu_2$, (ii) $s_{01} = s_{10}$ and (iii) that either $s_{11} = 1-(1-s_{01})^2$ (no epistasis, the 2 mutations have independent fitness effect) or $s_{11} = s_{01} = s_{10}$ (high negative epistasis, the second mutation had no further fitness effect), we apply the formula to assess value of θ when the wild-type variant must acquire 2 mutations to break the resistance down for s_{01} and s_{10} varying from very low (10^{-3}) to large (1) selective disadvantage and $\mu_1 = \mu_2 = 10^{-4}$.

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